

Original
articleEuropean course on HPV associated pathology:
guidelines for primary care physicians for the
diagnosis and management of anogenital warts

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The European Course on HPV Associated Pathology (ECHPV) was founded in 1990 by a group of clinicians, pathologists, and virologists to teach important principles for the practice and management of human papillomavirus (HPV) disease to gynaecologists, dermatologists, and other medical disciplines. These guidelines are intended to assist the practice of primary care physicians for diagnosis and treatment of anogenital warts.

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Aetiology

Condylomata acuminata “condylomas” are benign anogenital warts caused by human papillomavirus (HPV), genotypes 6 and 11 being found in >90% of cases.¹ Patients with visible warts may be infected simultaneously with oncogenic “high risk” HPVs such as types 16 and 18, which mostly give rise to subclinical lesions associated with intraepithelial neoplasia (IN) and anogenital cancer.^{1–3}

Lesional features**MULTIFOCAL OCCURRENCE**

Lesions tend to appear in areas that are traumatised during intercourse⁴ and may be solitary but generally comprise from 5 to ≥ 15 lesions of 1–10 mm diameter. Warts may coalesce into large plaques, which is particularly common in immunosuppressed individuals and in diabetics.

In uncircumcised men, the preputial cavity (glans penis, coronal sulcus, fraenum, inner aspect of the foreskin) is most commonly affected, while in circumcised men the shaft of the penis is often involved.⁵ Warts may also occur on the scrotum, groin, perineum, and anal area. In females, lesions affect the fourchette, labia minora, labia majora, clitoris, urethral meatus, perineum, anal region, vestibule, introitus, hymen, vagina, and ectocervix.^{2–6} The urethral meatus is affected in 20–25% of males and 4–8% of females.^{2–4} Anal warts are seldom found proximal of the dentate line. Intra-anal warts are most common when receptive anal intercourse has been practised.⁷

MULTIFORM MORPHOLOGY

Colour varies from pinkish raspberry to salmon red (non-keratinised warts), greyish white (heavily keratinised lesions), and ashen grey to brownish black (pigmented lesions). Condylomas tend to be non-pigmented but, if they are, they are mostly seen on pigmented skin (labia majora, penile shaft, pubis, groin, perineum, and anal area).^{8–9}

LESIONAL TYPES

Condylomas can be distinguished into three major types:

- *Acuminate warts* predominate on mucosal epithelium, such as the preputial cavity, urinary meatus, labia minora, introitus, vagina, cervix, anus, and anal canal, but may affect intertriginous areas as well (groins, perineum, and anal area). These digitate projections have highly vascularised dermal cores producing typical punctuated and/or loop-like patterns unless the vessels are hidden beneath pronounced keratinisation.
- *Papular warts*, being most common on keratinised epithelium (outer foreskin, penile shaft, scrotum, lateral vulva, pubis, perineum, and perianal area), are often hyperkeratotic or pigmented, lack the finger-like surface irregularities of acuminate warts, and are associated with differential diagnostic considerations. Pigmented, leucoplakia-like and brownish red papules signify bowenoid papulosis.
- *Macular lesions* may reveal their presence on mucous membranes because of subtle colour variations such as greyish white, pinkish red, or reddish brown.

INTRAEPIITHELIAL NEOPLASIA: BOWENOID PAPULOSIS AND BOWEN'S DISEASE¹⁰

Bowenoid papulosis (BP) and Bowen's disease (BD) are visible lesions associated with oncogenic HPV types, most commonly HPV 16, that exhibit full thickness intraepithelial neoplasia (IN-III). These conditions are distinguished on clinical grounds, patient age being most important; BP appears at 25–35 years and BD at 40–50 years or over. BP presents as maculopapular lesions exhibiting a smooth velvety surface; the colour tone on mucous membrane sites is brownish or salmon red, greyish white, and on cutaneous sites ashen grey to brownish black.^{8–11}

“GIANT CONDYLOMA” (BUSCHKE-LOEWENSTEIN TUMOUR)

This is a very rare variant of HPV 6 and 11 associated disease, characterised by aggressive downgrowth into underlying dermal struc-

tures. A complex histological pattern may exist with areas of benign condyloma intermixed with foci of atypical epithelial cells or well differentiated squamous cell carcinoma. Diagnosis of Buschke-Loewenstein tumour often requires multiple surgical biopsies, computed tomography, or magnetic resonance imaging.⁹

Physical and psychosexual implications

Anogenital warts are disfiguring and can impact sexual lifestyle. They cause feelings of anxiety, guilt, anger, and loss of self esteem and create concerns about future fertility and of cancer risk.¹²⁻¹³ Physical symptoms may include inflammation, fissuring, itching, bleeding, or dyspareunia.⁹

Clinical evaluation

The goal of investigation is to ensure appropriate diagnosis and treatment and to minimise psychosexual sequelae. By removing the disease, the risk of transmission of HPV for that individual is probably reduced. Tests for concurrent STDs should be offered according to local policy. Before therapy, recording the distribution of solitary, multiple, or plaque lesions at various sites allows for subsequent evaluation of clearing of original lesions and the identification of any new lesions that develop.

In both sexes a careful inspection of the outer genitals is performed with a clear and powerful light. Use of a lens is highly recommended to detect small lesions.

In women 25% also have acuminate cervical and/or vaginal warts; up to 50% flat lesions or cervical intraepithelial neoplasia (CIN) lesions, the majority being low grade.²⁻³ About one third of women with vulval intraepithelial neoplasia (VIN) have associated CIN and/or vaginal intraepithelial neoplasia (VAIN).¹⁴⁻¹⁵ Accordingly, all women with anogenital warts should have a speculum examination to identify the presence of coexisting vaginal and/or cervical warts. In order to detect flat lesions cytology and/or colposcopy can be used. Colposcopy has a higher sensitivity, especially for low grade CIN. In contrast with vulvar lesions, routine histology assessment is mandatory whenever cervical lesions are treated, the biopsy being taken under colposcopic guidance.

Diagnosis—key points

- Routine histology is unnecessary for newly occurring, multiple, acuminate warts in patients younger than 35 years
- Differential diagnostic aspects generally exist for papular and macular lesions, as well as for warty lesions in patients over the age of 35–40, when routine biopsy is encouraged
- HPV typing of anogenital warts does not add information of clinical use
- The acetic acid test may be valuable for delineation of disease before biopsy and surgical treatment

MEATOSCOPY

The meatal lips can be everted using cotton wool swabs but a fuller inspection of the fossa navicularis in men is performed by “meatoscopy” using a small speculum (spreader) or an otoscope; about 5% of cases require urological investigation for adequate delineation of the proximal border. As a rule, the posterior urethra of male patients is not involved without previous or simultaneous growth of meatal warts.

PROCTOSCOPY

Concurrent perineal and perianal warts exist in one third of patients, when anoscopy is indicated.

ACETIC ACID TEST¹⁶

Following application of 5% acetic acid, HPV lesions may turn greyish white for a few minutes. As the test has poor specificity it is only recommended for use in specialist settings where colposcopy is available, and is not recommended for screening purposes. However, it may be valuable in identifying lesions for targeted biopsy and for demarcating lesions during surgical therapy. False positive results are commonly due to inflammatory conditions (for example, lichen sclerosus et atrophicus, lichen planus, psoriasis, balanoposthitis and vulvovaginitis, eczema, genital herpes, and traumatic microabrasions) and give rise to ragged, irregular acetowhite borders. There may be varying degrees of underlying hyperaemia and capillaries lack the vascular punctuation suggestive of HPV.

Histology

Biopsy is unnecessary for newly occurring, multiple, acuminate lesions but is recommended in atypical cases for differential diagnostic purposes or in any cases where the benign nature of a papular or macular lesion is unclear such a conspicuous bowenoid papulosis, Bowen's disease and giant condylomas.

Biopsy is performed under local infiltration anaesthesia, preferably 10 minutes after applying topical anaesthesia, using a punch biopsy, an excision technique, or biopsy forceps.

Differential diagnosis

Differential diagnoses include a range of dermatological conditions including molluscum contagiosum, fibroepitheliomata, and seborrhoeic keratoses.⁸⁻⁹⁻¹⁶ However, the most frequent condition causing confusion in males is physiological pearly penile papules developing in adolescent men, when 1–3 rows of discrete non-coalescing 1–2 mm papules appear circumferentially on the verge of the glans and/or symmetrically in the parafoveal area. They are small, the surface is smooth, do not coalesce, and do not show the vascular pattern of condylomas. In females, condylomas must be distinguished from physiological regularly shaped and non-coalescing, mostly symmetrical papillae appearing on the inner surface of the labia minora and in the vestibule (“micro-papillomatosis labialis”). Sebaceous glands of the foreskin and vulva are also often seen in

normal individuals as multiple, discrete, greyish yellow, non-indurated lesions on the inner aspect of the prepuce and labia minora.

Treatment

A reasonable expectation of therapy is cure, or at least long lasting remission from warts and/or symptoms. The principal shortcoming of available therapies is that no method necessarily eradicates warts, maintains clearance, and eliminates the virus; recurrence rates, including new lesions at previously treated or new, remote sites, are often 20–30%. All therapies are associated with local skin reactions including itching, burning, erosions, and pain. Some regimens require multiple physician office visits and, thus, are not convenient for the patient.

TREATMENT RECOMMENDATIONS

In the formulation of these guidelines we have reviewed and considered those produced recently by national groups in the United Kingdom and United States.^{17–18} We have also evaluated the evidence that supports our treatment recommendations using grades developed by the Agency for Health Care Policy and Research (see tables 1 and 2).¹⁹ Our recommended treatment modalities are:

Home therapy

- Podophyllotoxin (0.15% cream or 0.5% solution)
- Imiquimod (5% cream).

Office therapy

- Electrosurgery/laser/curettage/scissors excision
- Cryotherapy
- Trichloroacetic acid.

Clinicians who treat patients should be knowledgeable about, and have available, at least one home therapy and one office therapy. Choice of therapy depends on the morphology and extent of warts and should be made by mutual agreement between the physician and the patient. The average patient has a relatively small number of warts that can eventually be eliminated with most treatments. Patients with limited disease (1–5 warts) may benefit from

simple office therapy. As warts regress spontaneously in some patients, no treatment is an option for warts at any site.

HOME THERAPY

1 Podophyllotoxin 0.5% solution and 0.15% cream (1b, A)

Podophyllotoxin, a purified extract of the podophyllum plant, binds to cellular microtubules, inhibits mitotic division, and induces necrosis of condylomas that is maximal 3–5 days after administration. Erosions occurring as the warts necrotise are shallow and heal within a few days.^{20–21}

Each course of podophyllotoxin treatment comprises self application twice daily for 3 days, followed by 4–7 rest days. Use of 0.5% podophyllotoxin solution is convenient for penile warts. However, vulvar and anal warts are more feasibly and efficiently treated with 0.15% podophyllotoxin cream when digital self examination and tactile sensations facilitate the application procedure.

In uncircumcised males 70–90% of acuminated warts disappear after 1–2 courses of 0.5% podophyllotoxin solution, and 60–80% of patients become free of penile warts after 1–4 courses.^{20–22} Efficacy from the solution is lower for females and circumcised males, who experience a complete cure in less than 50% of cases.^{23–25} Clearance rates from 0.15% podophyllotoxin cream against vulval and anal warts are 60–80% when patients treat themselves for 1–4 courses.^{26–28} The recurrence rates with podophyllotoxin preparations are in the range of 7–38%.^{23–25} Warts that have not resolved after four courses should be treated by alternative means. Urinary meatus warts and warts on keratinised skin are often refractory.²²

Up to 50–65% of patients using podophyllotoxin experience transient and acceptable burning, tenderness, erythema, and/or erosions for a few days when the warts necrotise.^{21–22} Side effects are usually only associated with the first course of therapy.²² Occasionally, some pain occurs and uncircumcised men may experience transient problems in retracting the foreskin.²¹

Table 1 Levels of evidence¹⁹

Level	Type of evidence (based on AHCPR 1992)
Ia	Evidence obtained from meta-analysis of randomised controlled trials
Ib	Evidence obtained from at least one randomised controlled trial
IIa	Evidence obtained from at least one well designed controlled study without randomisation
IIb	Evidence obtained from at least one other type of well designed quasiexperimental study
III	Evidence obtained from well designed non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

Table 2 Grading of recommendations¹⁹

Grade	Recommendation (based on AHCPR 1994)
A (evidence levels Ia, Ib)	Requires at least one randomised, controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation
B (evidence levels IIa, IIb, III)	Requires availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation
C (evidence level IV)	Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable studies of good quality

Treatment—key points

- First line treatment will achieve clearance in most patients within 1–6 months, although disease persists in up to one third of patients
- Home therapy can be proposed in most cases as first line therapy for a first attack of acuminata warts. Acuminata warts respond in up to 90% but papular and macular lesions in only 50% of cases
- Few, small lesions can be easily treated under local anaesthesia by scissors excision, diathermy, cryotherapy, or TCA
- TCA should not be used on large lesions and multiple sessions are not well tolerated by patients
- Lesions occurring at new sites during treatment or after clearance, do not necessitate a change of the treatment modality
- Persistence or reappearance of the treated lesion is usually an indication to switch to another treatment modality
- Patients should be evaluated regularly until the warts are cleared
- Patients should be informed that periods of coital rest throughout the course of the therapy might reduce therapy related symptoms such as pain or discomfort.

2 Imiquimod cream, 5% (Ib, A)

Imiquimod (imidazoquinolinamine) is a nucleoside-like compound that by topical application to warts acts as an immune response modifier, inducing local production of α and γ interferon and recruitment of immune cells including CD4+ T cells. This process may be followed by an immune induced wart regression which is accompanied by a reduction in HPV DNA.^{29 30}

Imiquimod cream, supplied in single use sachets, is applied to the warts three times a week at bedtime and the area washed with mild soap and water the next morning. Treatment continues until wart clearance, or for a maximum of 16 weeks. Local reactions at the treatment site may occur and a rest period of several days may be taken if required.

In the pivotal clinical study, wart clearance was achieved by 56% of patients.³¹ More women (77%) than men (40%) cleared their warts, the male study population comprising predominantly circumcised men.³¹ Females had a shorter median time to clearance (8 weeks) compared with males (12 weeks). A low recurrence rate (13%) was found.³¹

The most common adverse reaction seen with imiquimod use is erythema which occurred in 67% of patients in the pivotal clinical study, most of them mild to moderate in intensity.³¹ Only 1% of patients discontinued therapy due to local skin/application site reactions.³¹ However, in a more recent European study in uncircumcised males, reporting a clearance rate of 62% after 13 weeks of therapy, it was noted that 29% of the men required drug free rest period(s) and that 6% discontinued due to erosions and/or burning.³²

Contraindications for and problems associated with home therapy

Podophyllotoxin is contraindicated during pregnancy and women of childbearing age must use contraception or abstain from penetrative sexual activity during therapy. No studies have been conducted with imiquimod in pregnant women but the drug has not been found to be teratogenic in animal studies.

Skin reactions to podophyllotoxin generally develop on day 3 of therapy and to imiquimod, after 3–4 weeks. Most resolve spontaneously within a drug free period of a few days.

A rare but important complication is difficulty in retracting the foreskin because of painful erosions or oedema when treating multiple warts in the preputial cavity. Patients should be advised to return for medical supervision if this occurs. Daily symptomatic office therapy includes using saline rinses and a topical corticosteroid cream applied liberally under the foreskin until improvement.

OFFICE THERAPY**1 Surgical treatment**

It is not possible to give clear directions for the surgical method of choice, as this is a matter of wart distribution, local tradition, and the clinical skills and experience of the physician. Surgery may be used as primary therapy, and the majority of patients can be treated under local anaesthesia. Routine use of local anaesthetic cream for 10–15 minutes is recommended before infiltration anaesthesia, reducing discomfort from injections significantly. Use of up to 100 mg lignocaine (lidocaine, as 5 ml of 2% or 10 ml of 1%) for infiltration gives rapid anaesthesia of the epithelium. Adrenaline as adjuvant reduces any bleeding but is contraindicated on the penis and in the clitoris region. Infiltration anaesthesia leads to separation and elevation of exophytic lesions facilitating accurate removal and sparing of uninvolved skin bridges for an optimal re-epithelialisation process to follow. The end-point for the removal of tissue is the view of the underlying papillary dermis, which has a tanned chamois leather-like character. More excessive destruction may lead to fibrosis and scarring. When performed carefully, simple surgical approaches leave highly satisfactory cosmetic results, with the exception of some depigmentation, which is disadvantageous on very pigmented skin.

All lesions treated properly by surgery virtually disappear. However, regardless of the technique, 20–30% of patients will develop new lesions at the borders of the treated tissue and/or at remote sites.^{33 34}

(a) *Scissors excision (Ib, A), electrosurgery (Ib, A) and laser surgery (IIa, B)*—Superficial scissors excision is useful when only a few lesions are present and may be assisted by diathermy to control bleeding and to destroy any conspicuous wart tissue remaining after the excision.

Modern electrosurgical units utilise monopolar systems, where the electric current flows from the active electrode, the ball or the loop, through the patient's body to the return pad of the electrode.

Carbon dioxide laser emissions are in the infrared range. The energy emitted is focused to a specific spot by a system of mirrors and lenses, and is strongly absorbed by all types of tissue. Since total absorption of the carbon dioxide energy occurs in about 0.1 mm of the skin, very high power densities can be attained in small tissue volumes.

Patient counselling—key points

- Patients should receive clear information, preferably written, as to the cause, treatment, outcomes, and possible complications of anogenital warts
- Reassure patients that although wart clearance may take 1–6 months and recurrences may occur, complete clearance will occur sooner or later
- Smokers with recalcitrant lesions should stop smoking as a correlation exists with wart development⁴⁹
- Advise female patients about regular participation in cervical cytology screening programmes. Reassure that risk of cervical cancer is low and ample time exists for detection and removal of any CIN
- Encourage patients to use barrier protection with new sexual contacts until successful treatment has been completed. The use of condoms within a stable relationship may not be needed as the partner will already have been exposed to the infection by the time of consultation. Condom use does not influence the outcome of HPV associated morbidity once infection has become established in the individual
- Owing to long latency periods after transmission, the development of condylomas in only one partner in a steady relationship does not inevitably signify sexual contact outside that relationship
- Current partners and, if advisable, other partners within the past 6 months, should be assessed for the presence of lesions and for education and counselling about STDs and their prevention

Both electrosurgery and laser surgery should be performed with the use of surgical masks by the treatment team, and a smoke evacuator is required.

(b) *Formal surgery*—Extensive warts on the foreskin are sometimes best managed by circumcision rather than by other therapies, which may be associated with the risk of phimosis. Extensive intra-anal warts are most conveniently removed under general anaesthesia by a proctologist. Also, in children and sensitive patients with extensive warts on the vulvoanal area general anaesthesia may be preferred for surgical procedures.

2 Cryotherapy (Ib, A)

The mechanism of action of cryotherapy is through epidermal and dermal necrosis and thrombosis of the dermal microvasculature. Treatment is usually performed at weekly intervals, a freeze-thaw-freeze technique used at each session. Open application of liquid nitrogen can be performed either by spray device or by direct swab application, freezing the lesion and a margin of healthy skin for about 20 seconds. Closed cryoprobe systems utilise circulation of carbon dioxide, nitrous oxide, or nitrogen, the probe gently pressed to the surface moistened with saline or lubricating jelly and freezing performed until a freezing “halo” occurs a few millimetres around the lesion.

Cryotherapy has the advantages of being simple, inexpensive and rarely causes scarring or depigmentation. Clinical studies report an efficacy range of 63–89%.^{35–36} However, application techniques are difficult to standardise and repeated sessions are often required.

3 Trichloroacetic acid (TCA) 80–90% solution (Ib, A)

TCA is a caustic agent that causes cellular necrosis. It is applied directly to the wart

surface with a cotton tip applicator. It is most suitable for small acuminate or papular warts but less efficacious for keratinised or large lesions. The initial response rate is 70–81% but recurrence rate is up to 36%.^{17–37–38} Multiple applications at 1–2 weekly intervals may be required but repeated therapy is not well tolerated because intense burning may be experienced for up to 10 minutes after applications. TCA is extremely corrosive and overzealous use may cause excessive pain, deep ulcerations into the dermis, and scarring. A neutralising agent (for example, sodium bicarbonate) should be readily available in case of excess application or spills. When used optimally, a shallow ulcer forms that heals without scarring. TCA can be used safely during pregnancy.

THERAPIES NOT GENERALLY RECOMMENDED

Because of several shortcomings including low efficacy and toxicity problems, routine use of interferons, 5-fluorouracil, or podophyllin is not recommended for use in the primary care setting. In the specialist setting, 5-fluorouracil is sometimes used against urethral warts³⁹ and interferons alfa and beta as adjuvant to surgery in problem cases.^{40–41} Podophyllin 20–25%, a non-standardised resin extract from the *Podophyllum* plant, is inexpensive to produce but is associated with only moderate efficacy and appears to possess mutagenic properties in vitro.^{20–42–44} However, the in vivo implications of this finding are yet to be elucidated. Rarely, systemic toxicity has been described; applied in larger volumes severe systemic intoxication with fatal outcome has occurred leading to bone marrow suppression, CNS influence, and cardiovascular crisis.^{45–48}

PATIENT COUNSELLING

Information and counselling are fundamental to proper management and need to be non-judgmental, supportive, and focus on the nature of the disease, therapy expectations, and a balanced perspective on sexual issues.¹³

Referrals to specialists

The majority of anogenital warts can be dealt with by the non-specialist, both in terms of investigation and treatment. Referral to specialists is recommended as outlined in table 3.

In early pregnancy warts may enlarge and multiply.⁵⁰ Genital warts present at delivery are associated with a risk quoted at 1 in 400 of the infant developing juvenile laryngeal papillomatosis (JLP).⁵¹ There is no proof that treatment diminishes this risk, although reduction of viral burden would seem wise.

Immunosuppression, as consequence of HIV infection, and iatrogenically, as a result of transplant grafting, is linked to a significant increase in multicentric and refractory condylomas, and of intraepithelial neoplasia.^{52–53} The US CDC recommends annual cytological screening of HIV positive women. We advocate the same policy for allografted women.

Genital warts in children may result from several modes of transmission⁵⁴: acquisition at birth by HPV transmission from the maternal genital tract, autoinoculation from finger warts,

Table 3 Referral to specialists

Problem	Specialist
• Children	• Paediatrician • Multidisciplinary team
• Intraepithelial neoplasia • Vaginal warts	• Gynaecologist/urologist/proctologist/dermatologist with training in colposcopy
• Pregnant women	• Obstetrician
• Large widespread warts • Protracted course • Differential diagnostic problems	• Dermatovenereologist • Genitourinary medicine specialist • Gynaecologist
• Intraurethral warts	• Urologist
• Anal warts	• Dermatovenereologist • Proctologist
• Immunosuppression	• Dermatovenereologist • Gynaecologist

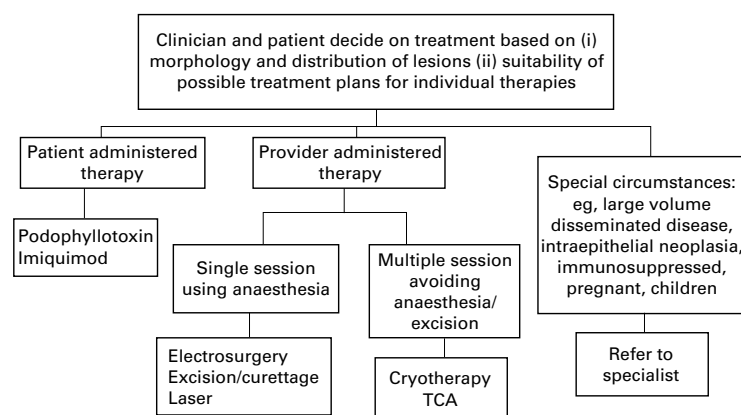


Figure 1 Algorithm for the treatment of external anogenital warts in the primary care setting.

and non-sexual transmission from family members/carers. However, the potential of sexual abuse must always be borne in mind; in one large series child abuse was documented in 43% of the cases of genital warts.⁵⁵ Children with anogenital warts should therefore be managed by a multidisciplinary team that includes a paediatrician.

Summary

A wide range of therapies is available for the treatment of external genital warts. Some can be applied by the patient at home and others by the healthcare provider. The choice of therapy depends on the morphology and extent of the warts, the experience of the caregiver and the preference of the patient.

The algorithm (Fig 1) summarises our recommendations for therapy in the primary care environment. Irrespective of the therapy used, HPV may persist in the adjacent tissues, resulting in recurrences and the need for further courses of treatment. Such cases should be referred to a specialist, when colposcopically guided surgery and adjuvant interferon are further options.

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